26. (New) A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of:

delivering to a tumor cell which has lost by mutation or deletion a wild type therapy sensitizing gene activity, an exogenous gene conferring said wild type therapy sensitizing gene activity,

effecting the expression of said wild type therapy sensitizing gene activity in said tumor cell, and

subjecting said tumor cell to said cancer therapy.

27. (New) The method of claim 26, wherein said exogenous gene is selected from the group consisting of p53, Rb and fas.

28. (New) The method of claim 26, wherein said exogenous gene is p53.

REMARKS

The specification has been amended to correct informalities as suggested by the Examiner. Claims 21 and 22 have been canceled without prejudice to future prosecution thereof. Claims 1-3, 6, 9, 10, 12-15, 17-20, and 23 have been amended. New claims 24-28 are added. Applicant submits that no new matter is added with these amendments.

Claims 1-20, and 23-28 are pending in the present application.

I. Amendments Made In Response To The Examiner's Suggestions

Following the Examiner's suggestions made in a telephonic interview on September 19, 1996, the definition of "therapy sensitizing gene activity" and claim 1 have been amended. The amended claim 1 recites a method directed to a tumor cell which has lost by mutation or deletion its wild type p53 gene. The Examiner stated in the interview that these amendments would overcome the rejections under 35 U.S.C. § 112, first paragraph.

To reflect the breadth of the invention before claim 1 was amended, new claim 26 is added to recite a method directed to a tumor cell which has lost by mutation or deletion a wild type therapy sensitizing gene activity.

Claim 2 has been amended to make it an independent claim because the amended claim 1 is no longer a genus claim to claim 2.

Claim 9 has been amended to break up the Markush group into three with one remaining in claim 9 and the other two going to new claims 24 and 25.

II. The Section 112 Rejections

The Examiner rejected claims 1-23 under 35 U.S.C. § 112, first paragraph, as allegedly not containing a written description of the claimed invention. This rejection is respectfully traversed.

The Examiner also rejected claims 1-23 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant submits that the amendments to claims 1-3, 6, 9, 10, 14, 15, and 17-20 have rendered these rejections moot.

Accordingly, it is respectfully requested that the rejections against claims 1-23 under 35 U.S.C. § 112, first and second paragraphs be withdrawn.

A. The written description requirement is not relevant to the issues raised in the final office action

"Adequate description of the invention guards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath Inc. v. Mahurkar, 19 U.S.P.Q.2d, 1111, 1115 (Fed. Cir. 1991). Thus, the real issue on written description cases is whether the claims are entitled to the benefit of the application's original filing date.

"The description requirement comes into play only when a claim is added by an applicant for a patent at some stage after the original filing date and the claim differs in scope from the original claims." 2 Donald S. Chisum, PATENTS § 7.04 at 7-137 (Rel. 52, 1994). The Manual of Patent Examining Procedure § 2163.03 lists four circumstances where adequate written description issue arises, none of which applies to this case. Numerous cases and the MPEP hold that original claims constitute their own description, and later added claims of

similar scope and wording are described thereby. In re Koller, 204 U.S.P.Q. 702, 706 (CCPA 1980).

In this case, the amended claims describe substantially the same invention as originally filed, i.e. a method of increasing the therapeutic effect of a cancer therapy by delivering a wild-type therapy sensitizing gene activity to a tumor cell that has lost such activity. In fact, the Examiner did not argue that the amended claims are of different scope from those originally filed in his written description rejection. Rather, the Examiner focused on the unpredictability of using a DNA encoding p53 to treat all types of cancers, which is not relevant to the written description requirement.

B. It is improper to masquerade a utility rejection as a written description rejection

The Examiner stated on page 11 of the final office action that "The rejection is not one for lack of utility but for inadequate written description of the invention." However, throughout the written description rejection, the Examiner expressed his doubt of the usefulness of the claimed invention.

For example, on page 3 of the final office action, the Examiner stated:

> even when DNA encoding p53 is expressed, it is apparently ineffective in altering the neoplastic properties of the cell [citing Chen et al.] ... thus, there is ***doubt*** created in the art that the DNA encoding p53 would be effective in all cancers ...

On page 4 of the final office action, the Examiner stated that "here the specification creates its own ***doubt*** as to the predictability of the using even the DNA encoding p53 in treating all types of cancers ...".

On page 5 of the final office action, the Examiner stated:

> Here, there is further ***doubt*** as Ullrich et al. (Oncogene, vol 7) indicate (page 1641) that there may be different p53 mutants that exert a stronger dominant negative effect *in vivo* than other mutant forms of p53, in which case, wild-type p53 may not be able to exert an antiproliferative effect under any circumstances ...

On page 6 of the final office action, the Examiner stated:

> thus, there is ***doubt*** created by the art that the DNA encoding p53 would be effective in all cancers as it is not indicated in the present specification that the DNA coding the therapy sensitizing properties of the p53 are in all DNA that encode a product made from that DNA that effect a therapy sensitizing function.

On page 10 of the final office action, the Examiner stated:

> Thus, it is apparent that others skilled in the art would not have accepted the assertions of therapeutic utility on the face of the instant written description in the absence of convincing scientific evidence given the ***doubts*** expressed in the cited references.

It is clear that the Examiner doubted the asserted utility of the claimed invention despite his assertion that the rejection is not one for lack of utility. Applicant submits that it is improper to cast the utility rejection as a written description rejection.

Applicant has set forth explanations in a response filed March 21, 1996 why there is credible utility for the claimed invention under the Examiner Guidelines For Biotech Applications by the Patent and Trademark Office.

Applicant has enclosed a recent publication by Roth et al. Nature Medicine 2(9):985-991 (September, 1996) which describes retrovirus-mediated wild-type p53 gene transfer to tumors of patients with lung cancer. This paper shows that wild type p53 gene can be transferred into human cancer cells *in vivo* and expressed there.

C. It is improper to limit Applicant's claims to those directed to p53

In the interview on September 19, 1996, the Examiner claimed that p53 is the only therapy sensitizing gene. In the contrary, Applicant submits that a therapy sensitizing gene includes genes other than p53.

For example, MLH1 and MSH2 are therapy sensitizing genes. The human colon cancer cell line HCT 116 has a mutation in MLH1 gene on human chromosome 3. HCT 116 cells have high tolerance to the chemotherapy drug, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). When a copy of wild type hMLH1 gene was delivered to HCT 116 cells by way of a normal human chromosome 3, it increased the sensitivity of HCT 116 cells to MNNG. *See*, Koi et al. Cancer Res. 54(16):4308-12, (1994), a copy of which is enclosed for Examiner's reference. Similarly, the transfer of wild type hMSH2 gene into the human endometrial cancer cell line HEC59, which expresses no hMSH2, increases the sensitivity of the cancer cells to cisplatin. *See*, Aebi et al. Cancer Res. 56(13):3087-90, (1996), a copy of which is enclosed for Examiner's reference. Therefore, to limit Applicant's claims to those directed to p53 would unduly restrict the scope of the present invention.

III. The Section 103 Rejection

The Examiner rejected claims 1-11, 17-20 and 22 under 35 U.S.C. § 103 as allegedly being obvious over Cheng et al. taken with Srivastava and Moossa et al.

The Examiner rejected claims 12-18, and 20 under 35 U.S.C. § 103 as allegedly being obvious over Cheng et al. taken with Srivastava and Moossa et al. and further in view of Wu et al., Malkin et al., and Chen et al.

The Examiner rejected claims 1-15, 17-20 and 22 under 35 U.S.C. § 103 as allegedly being obvious over Nabel et al. taken with Wu et al., Malkin et al., and Moossa et al.

The Examiner rejected claim 21 under 35 U.S.C. § 103 as allegedly being obvious over either of Cheng et al. taken with Srivastava and Moossa et al., or Nabel et al. taken with Wu et al., Malkin et al., and Moossa et al., and further in view of Itoh et al.

The Examiner rejected claim 23 under 35 U.S.C. § 103 as allegedly being obvious over either of Cheng et al. taken with Srivastava and Moossa et al., or Nabel et al. taken with Wu et al., Malkin et al., and Moossa et al., and further in view of Eppstein et al.

However, given the differences between the present invention and the references cited by the Examiner, the references fail to support a *prima facie* case of obviousness. These rejections are respectfully traversed.

A. Prior art cited by the Examiner does not describe or suggest whether wild type p53 would make a tumor cell more or less sensitive to a cancer therapy

Chen et al. expressed wild type p53 protein in a peripheral neuroepithelioma cell line (A673) that reduced the tumor cells' ability to form colonies in soft agar and tumors in nude mice.

Cheng et al. expressed wild type p53 protein in the human T leukemia cell line Be-13, which lacks endogenous p53 protein that reduced the growth rate of infected Be-13 cells *in vitro*, suppressed colony formation in methylcellulose cultures, and abrogated Be-13 cells' tumorigenic phenotype in nude mice.

Eppstein et al. described liposome formulations which can be used to transport DNA, RNA or polypeptide into cells.

Itoh et al. isolated cDNA encoding human Fas antigen determinant from human T cell lymphoma KT-3 cells. When they expressed the cDNA in murine T cell lymphoma WR19L or fibroblast L929, the transformed cells were killed by mouse anti-Fas antibody by apoptosis.

Malkin et al. described that alterations of the *p53* gene occur not only as somatic mutations in human cancers, but also as germ line mutations in some cancer-prone families.

Moossa et al. described conventional cancer therapies such as radiation therapy, chemotherapy, biological therapy, cryotherapy and hyperthermia.

Nabel et al. described delivering proteins to discrete blood vessel segments by catheterization using genetically modified or normal cells or other vector systems.

Srivastava described hybrid parvovirus vectors for gene therapy, e.g. delivering constitutive levels of a pharmaceutical product or producing a recombinant protein.

Wu et al. described a targetable gene delivery system for introducing foreign genes into mammalian cells utilizing receptor-mediated endocytosis.

In summary, although Chen et al. and Cheng et al. described tumor suppressive effects of wild type p53, no one could have made a prediction based on these two references and the other cited references by the Examiner whether wild type p53 would make a tumor cell more or less sensitive to a cancer therapy such as chemotherapy or radiation therapy.

B. The claimed invention is not obvious over the cited references when all the limitations of the claims are considered

When evaluating a claim for determining obviousness, all limitations of the claim must be evaluated. The invention must be reviewed as a whole. In re Gulack, 217 U.S.P.Q. 401 (Fed. Cir. 1983).

The present invention claims a process for improving the therapeutic effect of a cancer therapy such as chemotherapy or radiation therapy by increasing the sensitivity of cancer cells to the therapy. The sensitivity is increased by delivering a gene conferring wild type therapy sensitizing gene activity into a tumor cell which has lost its wild-type therapy-sensitizing gene activity. The tumor cell is then subject to the cancer therapy.

None of the prior art references cited by the Examiner described, either alone or in combination, that a gene or its encoded protein may be used to make a tumor cell lacking wild-type therapy sensitizing gene activity more sensitive to cancer therapy.

Malkin et al. described the prevalence of *p53* mutations in various cancer or pre-cancer cells but did not describe how to sensitize these cells to chemotherapy or radiation therapy.

Although Chen et al. described that wild type p53 protein reduced tumor cells' ability to form colonies in soft agar and tumors in nude mice and Cheng et al. described that wild-type *p53* reduced the growth rate of tumor cells *in vitro* and *in vivo*, they did not describe or suggest using wild-type *p53* to make the tumor cells more sensitive to chemotherapy or radiation.

Moossa et al. described conventional cancer therapies but did not describe or suggest that tumor cells can be made more sensitive to the therapies by transferring wild-type *p53* or other therapy sensitizing genes into the tumor cells.

Wu et al., Srivastava, Eppstein et al., and Nabel et al. described methods of delivering genes or proteins to cells but did not describe delivering wild type therapy sensitizing gene activity into tumor cells to sensitize them to cancer therapies.

Itoh et al. described cloning the Fas antigen and an antibody against the Fas antigen but did not describe delivering wild type Fax into tumor cells to sensitize them to cancer therapies.

C. No suggestion or motivation to make the claimed invention exists in the cited references

Where one element of the claimed invention is found in one reference, and another element of the claimed invention is found in another reference, the teachings of the two references can be combined only if there is some suggestion or incentive to do so. In re Fine, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988).

In addition, the motivation or suggestion for combining the teaching must be other than the knowledge learned from the disclosure of the applicant. In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989).

In this case, no suggestion or motivation was given in the prior art to combine the transfer of wild p53 into tumor cells with chemotherapy or radiation to increase the therapeutic effect of such therapy. The references cited in the final office action each described a part of the claimed process but they did not describe the whole process or suggest combining the parts to make the whole process. The only way the disclosures of Cheng et al. and other references cited by the Examiner can be read to result in the above statement is with benefit of applicant's disclosure.

Such use of applicant's disclosure would be improper in an obviousness analysis. Selective hindsight cannot be used to evaluate obviousness. There must be a reason or suggestion in the prior art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure. In re Dow Chem. Co., 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

The claimed invention is not obvious in view of Cheng et al. and the other cited references because they provided no indication that adding wild-type *p53* or any other therapy sensitizing gene activity to a tumor cell would sensitize the tumor cell to chemotherapy or radiation. Therefore, it is respectfully submitted that Cheng et al., Moossa et al., Wu et al., Srivastava, Nabel et al., Malkin et al., Chen et al., Eppstein et al., and Itoh et al. do not provide a *prima facie* case of obviousness.

D. The claimed invention provides an unexpected result

On page 15 of the final office action, the Examiner supports his obviousness rejections by arguing that Cheng et al. suggest therapeutic suppression of the unregulated growth of T-cell acute lymphoblastic leukemia (T-ALL) by introduction of the DNA encoding p53 into T-ALL cells. It appears that the Examiner equates the tumor suppression effect of wild type p53 with the therapy sensitization effect of wild type p53. Applicant submits that such equation is mistaken.

That p53 is a tumor suppressor, as reported in Cheng et al., does not lead one skilled in the art to conclude that p53 is a therapy sensitizer. On the contrary, the growth suppressive effects of p53 documented in Cheng et al. would lead one skilled in the art to expect it to render cells more resistant to therapy since chemotherapy and radiation therapy preferentially target growing cells.

Chemotherapeutic and radiation regimens presently employed for the treatment of cancer are known to work by killing cells undergoing rapid growth. Chemotherapeutic drugs and radiation are known to interfere with some aspect of the mitotic or cell cycle process required for cell growth and division. It is known in the prior art that cells that are not dividing or cycling or that are growing slowly tend to be less susceptible to chemotherapy and radiation.

By this conventional rationale, the expression of wild type p53 in tumor cells would be expected to reduce the sensitivity of the tumor cells to chemotherapy and radiation because wild type p53 slows or inhibits tumor cell growth. Indeed, Vogelstein et al., Cell 70: 523-526, (1992), stated that "**p53 mutations** may therefore constitute one of the few oncogenic alterations that **increase** rather than decrease the sensitivity of cells to antitumor agents."

Therefore, Applicant's discovery that wild type p53 sensitizes tumor cells to cancer therapy was unexpected from the prior art.

Unexpected or surprising results achieved by the claimed invention may be strong support for nonobviousness. Lindemann Maschinenfabrik v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). In this invention, the unexpected result of using wild type p53 gene to sensitize tumor cells to chemotherapy and radiation therapy is shown in Figures 1 and 2, and Examples 4 and 5 of the specification.

Figure 1 and Example 4 show that tumor cells transduced with wild type p53 are more sensitive to cisplatin treatment than tumor cells lacking wild type p53. Figure 2 and Example 5 show that tumor cells transduced with wild type p53 are more sensitive to radiation therapy than tumor cells lacking wild type p53.

None of these results was reported in or could be inferred from the references cited by the Examiner. Therefore, Applicant submits that the unexpected result obtained with the claimed method supports nonobviousness over references cited by the Examiner.

Accordingly, the claims are now in condition for allowance and a notice to that effect is respectfully requested. If the fee submitted in connection with this response is incorrect, please charge or credit Deposit Account No. 12-2475 for the appropriate amount.

Respectfully submitted,

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